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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,741	12/20/2001	Shinichiro Kurosawa	OMRF:004US/SLH	9903

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/028,741	KUROSAWA ET AL.	
	Examiner	Art Unit	
	Claire M Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The rejections of claims 17-30 are moot in view of the cancellation of the claims.

The rejection of claims 1 and 4-8 under 35 USC 102(b) is withdrawn in view of the amendment to the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 2, 3 and 9-16 remain and claims 1 and 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esmon et al. (Thrombosis and Haemostasis (1999 August) 82(2):251-258) and Kurosawa et al. (#C8, Blood (1998) 91:725-727) and in view of Hirsh et al. (#C6, Chest (1998 November) 114(5):445S-469S).

Esmon et al. teach a method of monitoring thrombin levels in patients undergoing anticoagulant therapy comprising the administration of hirudin, a specific thrombin inhibitor, by measuring circulating levels endothelial protein C receptor (EPCR), which receptors are necessarily soluble if circulating. Inhibition of thrombin by hirudin blocked increase in circulating EPCR (sentence bridging pages 254-255) in rats. Therefore, low levels of circulating EPCR corresponded to reduced levels of thrombin. Additionally, it was reported (p. 255, col. 2, third full sentence) that soluble EPCR (sEPCR)was present at high levels in the plasma of normal individuals and was increased several fold in patients with diseases associated with hypercoagulation (autoimmune disorders and septic shock, specifically systemic lupus erythematosus (see #C8, Kurosawa et al., Fig. 1)). It is concluded (p. 255, col. 2, first full paragraph) that "This [monitoring of plasma EPCR levels] could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these [human] patients."

Kurosawa et al., referenced by Esmon above, teach detection of sEPCR by ELISA in human patient blood plasma (Fig. 1). Tests showed that in patients with diseases often

complicated by thrombotic tendency and hypercoagulation, levels of sEPCR were significantly increased compared to normal control humans.

Hirsh et al. teach oral anticoagulant therapy for human patients with the anticoagulant Warfarin (*e.g.*, p. 446S, col. 1, second full sentence) and heparin (p. 463S, col. 2, second full paragraph). Also taught is the use of a vitamin K antagonist in anticoagulant therapy (p.445S, col. 2, middle of first full paragraph). Hirsh et al. also teach monitoring the effectiveness of anticoagulant therapy by measuring the prothrombin time (PT) as an international normalized ratio (INR, *e.g.*, Table 1 and section beginning at the bottom of p. 448S). Hirsh et al. points out that monitoring PT alone is not as reliable a measure of effectiveness of antithrombin therapy as the measure of both PT and INR (*e.g.*, p. 449S, col. 1, second to last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to monitor the effectiveness of anticoagulant therapy by measuring circulating sEPCR in human patients using the method of Esmon et al. and Kurosawa et al., because Esmon et al. teach that circulating sEPCR levels are decreased by administration of the anticoagulant hirudin and increased in hypercoagulation states and Kurosawa et al. teach that increased plasma sEPCR levels are associated with hypercoagulative states or risks. Also, the rodent experimentation of Esmon was conducted with the purpose of clinical application of the findings to humans. Therefore, the artisan of ordinary skill would have reasonably expected that the effects of an anticoagulant, including heparin or Warfarin taught by Hirsh et al., could have been adequately monitored by measuring circulating sEPCR levels. Further, since Hirsh et al. discussed the difficulties in using PT and INR for monitoring anticoagulation therapy effectiveness, one of ordinary skill in the art would have desired to use a more consistent measurement and one that involved testing a single thing (sEPCR) instead of multiple interacting things (PT and INR). Because vitamin K antagonists were known to be anticoagulants, it would have been obvious to include a vitamin K antagonist when thrombin levels or anticoagulation therapy were being monitored.

Applicant's arguments direct to the previous 35 USC 103 rejection pertain to the above recast rejection and are addressed here.

Applicants argue that the method of Esmon, who used a rodent model, is not predictive of the effectivenss of using the method with human patients. Applicants say that while animal models sometimes behave have the same as human patients, this is not always the case. The argument has been fully considered, but is not persuasive. As stated in the rejection above and in the previous Office action, it is concluded (p. 255, col. 2, first full paragraph) by Esmon et al. that "This [monitoring of plasma EPCR levels] could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these [human] patients." Further, Esmon et al. discuss mutations in the human thrombin gene in as a marker in some patients with myocardial infarction, who are 5 times more likely to have such a mutation than normal controls. Mutations in the thrombin gene can also lead to thrombosis in mice. "Taken together, these observation provide a firm clinical basis to conclude that the members of this pathway are critical to adequate negative regulation of the blood clotting system" (col. 2 of 252). Both the above conclusions support extending the rodent results to humans. Further, Giudici et al. (Haematologica, 1999, #C25 cited by Applicants) teaches that antithrombin infusion in animals receiving a lethal dose of *E. coli* provided a significant survival advantage. Simiarly, Giudici et al. also teaches that in a double-blind human study, administration of antithrombin conferred survival benefits to patients with severe sepsis and/or post-surgery complications (summarized in the second half of the Abstract).

Applicants argue that in, for example, experiments using an murine anti-TNFα mAb direct against recombinant human TNF there are different effects in monkey *vs.* human trials. The argument has been fully considered, but is not persuasive. First, it does not appear that the same antibody was used in each study (Hinshaw et al., #C27, mAb produced by Chiron; Fiedler et al., #C24, mAb produced by Cutter Biological; Tracey et al., #32, mAb produced by Tracey et al.; Abraham et al., #C20, produced by different lab). This is significant because different antibodies will bind different epitopes and have different activities/affinities. Also, experimental conditions are not identical. For example in the Abraham et al. clinical trial, patients with septic shock did have a trend in reduction in mortaility at 3 days post-infusion, though at 28 days post-infection there was no significant different in mortality between mAb and placebo patients. Fielder et al. did a short term experiment that ended after only 14 days. All animal studies were able to administer the mAb *before* or within hours of the introduction of the bacteria. This was

not possible for the humans. Tracey et al. found that baboons administered mAb one hour before bacterial infection were protected against shock but not organ failure. Complete protection was possible only when the mAb administration was 2 hours before infection. The studies cited by Applicants do not teach away from applying findings about coagulation in animal models compared to human patients. They only point out that one must keep in mind both the similarities *and* the differences in experimental protocol.

Applicants argue that protease activated receptors (PARs) are different in mice compared to humans, and that with the findings of Gu et al. (#C26) "one must question whether thrombin would be important for soluble EPCR generation in humans based on the Gu et al. (2000) report alone." The argument has been fully considered, but is not persuasive. Absent evidence to the contrary, mouse and human thrombin/coagulation systems are sufficiently similar for one to be used as a reasonable model for the other (see paragraph two above this). Fortunately, the art need not rely on the findings of Gu et al. alone, but has the teachings of others supporting the connection of sEPCR to thrombin and coagulation in humans and rodents.

Applicants argue that because there is more genetic variability in the human population compared to rats or mice, "even well-controlled animal studies can fall short of predicting clinical outcomes in humans." The argument has been fully considered, but is not persuasive. Genetic variability in the human population was illustrated by the inventors in a paper published after the effective filing date of the instant application and discussed in the "***Prior Art***" section in the previous Office action as follows:

> "...Stearns-Kurosawa et al., J. Thromb. Haemost. (2003 April) 1(4):855-856, teach that a bimodal distrubution of sEPCR is found in certain healthy populations (*e.g.*, those from Italy or France) and suggest that before using sEPCR as an indicator, gender and geographic location should be taken into account in determining what normal levels are. The latter reference suggests that that claimed invention may have inoperative embodiments, but this would be for a minority of the cases."

Variability in the human population does not mean animal models cannot be used for what the artisan of ordinary skill would expect for the human norm, even though there might be exception. Animal models are not relied upon as exact replicas for human responses, but serve such that results obtained from an animal model can be extrapolated to humans. Animal models have and continue to serve as valuable models for many human diseases/conditions.

Applicants argue that, "without the data provided in the instant application, one of ordinary skill in the art would not have been able to predict whether the work done in rats was reasonable predictive of the human clinical situation." The argument has been fully considered, but is not persuasive. It is maintained for the reasons of record and as discussed above that the artisan of ordinary skill would have accepted the rodent data for sEPCR as reasonably predictive of sEPCR behavior in humans.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

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Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
February 9, 2005

LORRAINE SPECTOR
PRIMARY EXAMINER